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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,394	07/28/1999	CHONG-JIN OON	56972/JPW/AK	6815

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EXAMINER	
WORTMAN, DONNA C	
ART UNIT	PAPER NUMBER
1648	19

DATE MAILED: 08/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/362,394	OON ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36 and 38-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-36 and 38-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The request filed on July 22, 2002, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/362394 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 20, 21, 26, 29, 30, 35, 36, 39, 41, 43, 44, 46-50, 52-54, 57-62, and 64-66 were amended and claim 37 was canceled. Claims 19-36 and 38-68 are pending and under examination.

The amendments to the specification and the claims to add SEQ identifiers are noted and are sufficient to comply with the sequence rules.

Applicant's amendments to the claims have overcome the rejections of claims 46-50, 52, 58-62, and 64 as previously made under 35 U.S.C. 112, second paragraph. As no amendments or remarks were directed to the interpretation of "has" in claims 43, 53, 54, 65 and 66, the recitation of "has" continues to be interpreted as open language.

Claims 19-35 are drawn to hepatitis B oligonucleotides that have a fluorescent dye, a fluorescein derivative, at the 5' end and that have a primary amine at the 3' end; claim 36 is drawn to a hepatitis B oligonucleotide that is linked to biotin at the 5' end; claims 38-41 are drawn to hepatitis B oligonucleotides that have a fluorescent dye, Texas red, at the 5' end; claims 42 and 43 are drawn to a hepatitis B oligonucleotide composition in which one oligonucleotide has a 5' biotin and one has a 5' fluorescent dye; claims 44-68 are drawn to methods for identifying hepatitis B viral nucleic acid sequences involving amplification of viral nucleic acid using PCR and hybridization of a fluorescent labeled amplification product to an immobilized fluorescent labeled probe.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite because it recites "primary amine" without clear antecedent since claim 32 depends from claim 27 which recites "primary amino." It is believed that "primary amine" is what was intended.

Claims 19-36 and 38-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/40193 to Stuyver et al., of record, in view of Guo et al. (Nucleic Acids Research 22(24):5456-5465, 1994, cited on PTO 1449, and of US Patent 6,100,030 to McCasky Feazel et al., cited on PTO 892, attached, and available under 35 U.S.C. 102(e). Stuyver et al. teach a method for detection of mutant HBV sequences in a sample comprising using primers, if necessary, to amplify the region(s) bearing mutations of interest and using appropriate specific probes, preferably about 10-25 nucleotides long, corresponding to the region bearing the mutation and its wild-type counterpart for hybridizing to the nucleic acids that are in the sample or are amplified from the sample. Fig. 1 presents nucleotide sequences for a number of HBV strains; sheet 4 of Fig. 1, e.g., discloses the nucleotide sequences that encode HBsAg and indicates the location of codon 145. Stuyver discloses solid supports, including beads or chips, for immobilizing oligonucleotide probes, and also discloses that the oligonucleotides may be modified in order to facilitate immobilization or in order to improve hybridization. Such modifications include homopolymer tailing, coupling with

reactive groups, or coupling to substances such as biotin. Oligonucleotides to be used as primers or probes may also be labeled. See, e.g., page 16, lines 5-20. Table 1, page 28 indicates examples of HBsAg primers (SEQ ID NO's 75, 76, 94, 104, 105) and probes for HBsAg codon 145 wild type and mutant sequences (SEQ ID NO's 77-82). Stuyver differs from the instant invention only in not disclosing specific fluorescent labels for the primers and probes, in not specifically disclosing a "C 7 primary amine" for immobilizing probes, and in not disclosing primers and probes identical in sequence to those instantly claimed in claims 20, 21, 26, 29, 30, 36, 39, 40, 43, 46, 47, 52, 53, 54, 58, 59, 64, 65, and 66. With respect to particular labels for primers used in amplification of sequences intended for later hybridization for genetic analysis, Guo et al. disclose DNA amplification using a set of primers, one of which has 5' biotin and one of which has a fluorescent label, fluorescein, where the biotin is to be used to separate the strands using streptavidin-coupled magnetic beads (see page 5457, DNA amplification and strand separation). Guo et al. also disclose hybridization sequences having polydT spacers and an aliphatic amino group at the 5' terminus (see, e.g., Fig. 1 and Table 1) to facilitate immobilization on glass supports. Neither Guo nor Stuyver specifically disclose an assay format involving two different fluorescent labels. McCasky Feazel et al. provide extensive background information regarding oligonucleotide hybridization assay formats, including those in which two different fluorescent labels are used, one on the 5' end of the amplified product and one on the 5' end of the immobilized probe. See, e.g., col. 23, lines 36-53 and col. 30, line 7-col. 31, line 34, listing, *inter alia*, Texas red and fluorescein derivatives as conventional and

widely known fluorescent labels, where the two labels are chosen to have appropriate characteristics. While the HBV primers and probes specifically disclosed by Stuyver are not identical to those instantly claimed, it would have been obvious to one of ordinary skill in the art to have selected other, similar, HBsAg primers and probes that include relevant portions of HBsAg in order to amplify the region including codon 145 and the sequences that encode the wild type and the escape mutant codon 145 based on the extensive teachings of Stuyver and to have successfully detected the mutation of interest, using the conventional formats and labels whose details are taught by Guo et al. and McCasky Feazel et al., because Stuyver teaches the importance of detecting HBV codon 145 mutations and teaches that amplification of viral nucleic acid by PCR and hybridization with immobilized probes, whose details are taught by Guo et al. and McCasky Feazel et al., are conventional methods for amplification and detection of specific sequences of interest.

To the extent that Applicant's remarks are seen to be applicable to the rejection now offered, those remarks will be addressed here.

Applicant has argued that no suggestion or motivation has been shown to attach any label of choice to the claimed oligonucleotides, particularly fluorescent labels, and that no reasonable expectation for success has been demonstrated for particular labels. Applicant has referred to Exhibits 3 and 4 in support of the assertion that different fluorescent labels have different properties in different environments and that different fluorescent dyes can alter the behavior of oligonucleotides, e.g., they can alter the mobility of labeled oligonucleotides. Applicant has pointed to various aspects of the

claimed subject matter which it is asserted are not taught by Stuyver et al., including HBV oligonucleotides with a fluorescent dye at the 5' terminus and a primary amine at the 3' terminus; compositions comprising two oligonucleotides, one with a biotin at the 5' terminus and one with fluorescent dye, specifically Texas red, at the 5' terminus; a method for identifying HBV surface antigen mutant 145 which comprises amplifying the nucleic acid in a reaction using two primers, one with a 5' biotin and one with a 5' fluorescent dye; and a method for identifying a wild type HBV surface antigen using two primers, one with a 5' biotin and one with a 5' fluorescent dye.

These arguments have been considered but not found persuasive. While Stuyver et al. do not specifically teach the fluorescent labels attached as claimed for the claimed purposes, Guo et al. and McCasky Feasel et al. do, and are cited for that teaching. Guo et al. also teach addition of an aliphatic amine (a "C 7 amine" as instantly claimed) for immobilizing oligonucleotides. With respect to the citation of Exhibits 3 and 4, it is appreciated that the properties of fluorescent dyes are affected by environmental conditions, and that a fluorescent dye can affect the mobility of an oligonucleotide in capillary gel electrophoresis; however, both Guo et al. and McCasky Feazel et al. teach appropriate fluorescent dyes to attach to oligonucleotides of interest to be used for PCR and hybridization as claimed, and support a reasonable expectation for success in those methods. Further, the effect of fluorescent labels on mobility in capillary gel electrophoresis is not seen to be particularly relevant to the present claims, since capillary gel electrophoresis is neither disclosed nor claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
August 5, 2002